REMARKS

Entry of the foregoing amendment is respectfully requested. By this amendment, five (5) typographical errors have been corrected and the claims have been amended to correct minor typographical errors therein. The foregoing amendment does not introduce new matter.

Enclosed herewith is a marked-up version of the changes made to the claims by this amendment. The enclosed pages are captioned "**Version with markings to show changes made.**"

Favorable action on the merits is earnestly solicited.

Respectfully submitted,
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CERTIFICATE OF MAILING

I certify that this amendment and enclosures are being deposited with the U. S. Postal Service with sufficient postage as first class mail in an envelope addressed to The Commissioner for Patents, Washington, D.C. 20231, on July 8, 2002.

Deborah A. Mojarro

Version with markings to show changes made

In the Specification:

Page 2, first full paragraph:

Recently, a cDNA (mRORγ orphan nuclear receptor) mRNA was isolated from a mouse muscle cDNA library (Medvedev, *et al.*, *Gene* 181:199-206 (1996); accession no. U43508; GI: 1155340). The 2066 bp cDNA encoded a protein of 516 amino acid residues, similar to the human 560 amino acid ROR (*see* Hirose, *et al.*, *Biochem. Biophys. Res. Commun.* 205:1976-83 (1994)). Furthermore, high sequence homology existed between the protein and human ROR gamma, with an overall identity of 88%. Analysis of the ROR gamma-response element using in vitro synthesized ROR gamma revealed that it binds as a monomer to response elements composed of a single core motif GGTCA preceded by a 6 bp AT-rich sequence. Northern blot analysis using RNA from different tissues showed that mROR gamma was found to be highly expressed in skeletal muscle, liver and kidney.

Page 6, third paragraph:

The term "target gene" (alternatively referred to as "target gene sequence" or "target DNA sequence" or "target sequence") refers to any nucleic acid molecule or polynucleotide of any gene to be modified by homologous recombination. The target sequence includes an intact gene, an exon or intron, a regulatory sequence or any region between genes. The target gene comprises a portion of a particular gene or genetic locus in the individual's genomic DNA. As provided herein, the target gene of the present invention is a RORγ gene. A "RORγ gene" refers to a sequence comprising SEQ ID NO:1 or comprising the sequence identified in Genebank as Accession No.: U43508; GI NO: 1155340. In one aspect, the coding sequence of the RORγ gene comprises SEQ ID NO:1 or comprises the RORγ gene identified in Genebank as Accession No.: U43508; GI: 1155340.

Page 52, first full paragraph:

2 clinically ill homozygous females (20774 and 20299) and 2 clinically ill homozygous males (19922 and 20294) had greatly elevated total white blood cell counts in which lymphocytes predominated. In one leukemic female 20774, lymphocytes were immature (blastic). This is consistent with a leukemic phase of lymphoma. Affected ~~mice~~ homozygous mice showed signs of illness, including poor grooming and hypoactivity. They had increased thoracic and abdominal

girth, hepatosplenomegaly, enlarged thymuses, and ascites; they appeared weak, scruffy, hunched, cachectic, lethargic, and have impaired respiration.

In the Claims:

Claims 17, 40, 42 and 46 have been amended as follows:

17. A transgenic mouse comprising a disruption in a RORγ gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: a spleen abnormality, a kidney abnormality, ~~a spleen abnormality~~ a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.

40. A method of producing a transgenic mouse comprising a disruption in a RORγ gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: a spleen abnormality, a kidney abnormality, ~~a spleen abnormality~~ a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones, the method comprising:

(a) introducing a RORγ gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a RORγ gene.

42. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a RORγ gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a RORγ gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: a spleen abnormality, a kidney abnormality, ~~a spleen abnormality~~ a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.

46. The method of claim 45, wherein the phenotype comprises at least one of the following: a spleen abnormality, a kidney abnormality, ~~a spleen abnormality~~ a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.